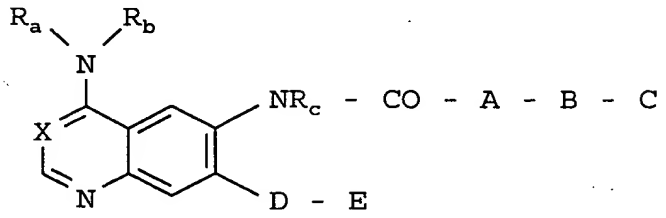
Patent Claims

1. Bicyclic heterocycles of general formula



, (I)

wherein

R_a denotes a hydrogen atom or a methyl group,

R_b denotes a phenyl, benzyl- or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3, while

R_1 and R_2, which may be identical or different, in each case denote a hydrogen, fluorine, chlorine, bromine or iodine atom,

a methyl, ethyl, hydroxy, methoxy, ethoxy, amino, cyano, vinyl or ethynyl group,

an aryl, aryloxy, arylmethyl or arylmethoxy group,

a methyl or methoxy group substituted by 1 to 3 fluorine atoms or

R_1 together with R_2, if they are bound to adjacent carbon atoms, denote a -CH=CH-CH=CH, -CH=CH-NH- or -CH=N-NH group and

R_3 denotes a hydrogen, fluorine, chlorine or bromine atom,

R_c denotes a hydrogen atom or a methyl group,

X denotes a methyne group substituted by a cyano group or a nitrogen atom,

A denotes a 1,1- or 1,2-vinylene group which may be substituted in each case by one or two methyl groups or by a trifluoromethyl group,

an ethynylene group or

a 1,3-butadien-1,4-ylene group optionally substituted by a methyl or trifluoromethyl group,

B denotes an alkylene or -CO-alkylene group wherein the alkylene moiety in each case contains 1 to 4 carbon atoms, while the linking of the -CO-alkylene group to the adjacent group A in each case must take place via the carbonyl group,

a -CO-O-alkylene- or -CO-NR_4-alkylene group wherein the alkylene moiety in each case contains 1 to 4 carbon atoms, while the linking to the adjacent group A in each case must take place via the carbonyl group, wherein

R_4 denotes a hydrogen atom or a methyl or ethyl group,

or a carbonyl group,

C denotes a 2-oxo-morpholin-4-yl group substituted by the group R_5 or by the group R_5 and a C_{1-4}-alkyl group, while

R_5 denotes a C_{3-4}-alkyl, hydroxy-C_{1-4}-alkyl, C_{1-4}-alkoxy-C_{1-4}-alkyl, di-(C_{1-4}-alkyl)-amino-C_{1-4}-alkyl, pyrrolidino-C_{1-4}-alkyl, piperidino-C_{1-4}-alkyl, morpholino-C_{1-4}-alkyl, 4-(C_{1-4}-alkyl)-piperazino-C_{1-4}-alkyl, C_{1-4}-alkylsulphanyl-C_{1-4}-alkyl, C_{1-4}-alkylsulphinyl-C_{1-4}-alkyl, C_{1-4}-alkylsulphonyl-C_{1-4}-alkyl, cyano-C_{1-4}-alkyl, C_{1-4}-alkoxycarbonyl-C_{1-4}-alkyl, aminocarbonyl-C_{1-4}-alkyl, C_{1-4}-alkyl-aminocarbonyl-C_{1-4}-alkyl,

di-(C_{1-4}-alkyl)aminocarbonyl-C_{1-4}-alkyl, pyrrolidinocarbonyl-C_{1-4}-alkyl, piperidinocarbonyl-C_{1-4}-alkyl, morpholinocarbonyl-C_{1-4}-alkyl or a 4-(C_{1-4}-alkyl)-piperazinocarbonyl-C_{1-4}-alkyl group,

a 2-oxo-morpholin-4-yl group substituted by two groups R_5, where R_5 is as hereinbefore defined and the two groups R_5 may be identical or different,

a 2-oxo-morpholin-4-yl group, wherein the two hydrogen atoms of a methylene group are replaced by a $-(CH_2)_m$, $-CH_2-Y-CH_2$, $-CH_2-Y-CH_2-CH_2$, $-CH_2CH_2-Y-CH_2CH_2$- or $-CH_2CH_2-Y-CH_2CH_2CH_2$- bridge optionally substituted by one or two C_{1-2}-alkyl groups, while

m denotes the number 2, 3, 4, 5 or 6 and
Y denotes an oxygen or sulphur atom, a sulphinyl, sulphonyl or C_{1-4}-alkylimino group,

a 2-oxo-morpholin-4-yl group, wherein a hydrogen atom in the 5 position together with a hydrogen atom in the 6 position is replaced by a $-(CH_2)_n$, $-CH_2-Y-CH_2$, $-CH_2-Y-CH_2CH_2$- or $-CH_2CH_2-Y-CH_2$- bridge, while

Y is as hereinbefore defined and
n denotes the number 2, 3 or 4,

or, if D together with E denotes a group R_d, it may also denote a 2-oxo-morpholin-4-yl group which may be substituted by 1 to 4 C_{1-2}-alkyl groups,

D denotes a -O-C_{1-6}-alkylene group, while the alkylene moiety is linked to the group E, or

an oxygen atom, while this may not be linked to a nitrogen atom of the group E, and

E denotes an amino group substituted by 2 C_{1-4}-alkyl groups, wherein the alkyl groups may be identical or different and each alkyl moiety may be substituted from the 2 position by a C_{1-4}-alkoxy or di-(C_{1-4}-alkyl)-amino group or by a 4- to 7-membered alkyleneimino group, while in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group may be replaced in the 4 position by an oxygen or sulphur atom or by a sulphinyl, sulphonyl- or N-(C_{1-4}-alkyl)-imino group,

a 4- to 7-membered alkyleneimino group optionally substituted by 1 to 4 methyl groups,

a 6- to 7-membered alkyleneimino group optionally substituted by 1 or 2 methyl groups, wherein in each case a methylene group in the 4 position is replaced by an oxygen or sulphur atom or by a sulphinyl, sulphonyl- or N-(C_{1-4}-alkyl)-imino group,

an imidazolyl group optionally substituted by 1 to 3 methyl groups,

a C_{5-7}-cycloalkyl group, wherein a methylene group is replaced by an oxygen or sulphur atom or by a sulphinyl, sulphonyl or N-(C_{1-4}-alkyl)-imino group, or

D together with E denotes a hydrogen atom,

a C_{1-6}-alkoxy group optionally substituted from the 2 position by a hydroxy- or C_{1-4}-alkoxy group,

a C_{3-7}-cycloalkoxy- or C_{3-7}-cycloalkyl-C_{1-4}-alkoxy group,

or a group R_d, where

R_d denotes a C_{2-6}-alkoxy group which is substituted from the 2 position by a C_{4-7}-cycloalkoxy- or C_{3-7}- cycloalkyl-C_{1-3}-alkoxy group,

a C_{4-7}-cycloalkoxy- or C_{3-7}-cycloalkyl-C_{1-6}-alkoxy group wherein the cycloalkyl moiety in each case is substituted by a C_{1-4}-alkyl, C_{1-4}-alkoxy, di-(C_{1-4}-alkyl)-amino, pyrrolidino, piperidino, morpholino, piperazino, 4-(C_{1-2}-alkyl)-piperazino, C_{1-4}-alkoxy-C_{1-2}-alkyl, di-(C_{1-4}-alkyl)-amino-C_{1-2}-alkyl, pyrrolidino-C_{1-2}-alkyl, piperidino-C_{1-2}-alkyl, morpholino-C_{1-2}-alkyl, piperazino-C_{1-2}-alkyl- or 4-(C_{1-2}-alkyl)-piperazino-C_{1-2}-alkyl group, while the abovementioned cycloalkyl moieties may additionally be substituted by a methyl or ethyl group,

while, unless otherwise stated, by the aryl moieties mentioned in the definition of the abovementioned groups is meant a phenyl group which may be mono- or disubstituted by R_6, while the substituents may be identical or different and

R_6 denotes a fluorine, chlorine, bromine or iodine atom, a C_{1-2}-alkyl, trifluoromethyl or C_{1-2}-alkoxy group, or

two groups R_6, if they are bound to adjacent carbon atoms, together represent a C_{3-4}-alkylene, methylenedioxy or 1,3-butadien-1,4-ylene group,

the tautomers, stereisomers and salts thereof.

2. Bicyclic heterocycles of general formula I according to claim 1, wherein

R_a denotes a hydrogen atom,

R_b denotes a benzyl or 1-phenylethyl group or a phenyl group substituted by the groups R_1 and R_2, while

R_1 denotes a hydrogen, fluorine, chlorine or bromine atom, a methyl, trifluoromethyl, cyano or ethynyl group and R_2 denotes a hydrogen or fluorine atom,

R_c denotes a hydrogen atom,

X denotes a nitrogen atom,

A denotes a 1,2-vinylene group,

B denotes a C_{1-4}-alkylene group,

C denotes a 2-oxo-morpholin-4-yl group substituted by the group R_5 or by the group R_5 and a C_{1-4}-alkyl group, while

R_5 denotes a C_{3-4}-alkyl, C_{1-2}-alkoxy-C_{1-4}-alkyl, di-(C_{1-2}-alkyl)-amino-C_{1-4}-alkyl, pyrrolidino-C_{1-4}-alkyl, piperidino-C_{1-4}-alkyl, morpholino-C_{1-4}-alkyl, 4-(C_{1-2}-alkyl)-piperazino-C_{1-4}-alkyl, C_{1-2}-alkylsulphanyl-C_{1-4}-alkyl, C_{1-2}-alkylsulphinyl-C_{1-4}-alkyl, C_{1-2}-alkylsulphonyl-C_{1-4}-alkyl, cyano-C_{1-4}-alkyl, C_{1-2}-alkoxycarbonyl-C_{1-4}-alkyl, aminocarbonyl-C_{1-4}-alkyl, C_{1-2}-alkyl-aminocarbonyl-C_{1-4}-alkyl, di-(C_{1-2}-alkyl)-aminocarbonyl-C_{1-4}-alkyl, pyrrolidinocarbonyl-C_{1-4}-alkyl, piperidinocarbonyl-C_{1-4}-alkyl, morpholinocarbonyl-C_{1-4}-alkyl- or a 4-(C_{1-2}-alkyl)-piperazinocarbonyl-C_{1-4}-alkyl group,

a 2-oxo-morpholin-4-yl group substituted by two groups R_5, while R_5 is as hereinbefore defined and the two groups R_5 may be identical or different,

a 2-oxo-morpholin-4-yl group, wherein the two hydrogen atoms of a methylene group are replaced by a $-(CH_2)_m$, $-CH_2-Y-CH_2$, $-CH_2-Y-CH_2-CH_2-$ or $-CH_2CH_2-Y-CH_2CH_2$-bridge, while

m denotes the number 2, 3, 4 or 5 and
Y denotes an oxygen or sulphur atom, a sulphinyl, sulphonyl or C_{1-2}-alkylimino group,

a 2-oxo-morpholin-4-yl group, wherein a hydrogen atom in the 5 position together with a hydrogen atom in the 6 position is replaced by a $-(CH_2)_n$, $-CH_2-Y-CH_2$, $-CH_2-Y-CH_2CH_2-$ or $-CH_2CH_2-Y-CH_2-$ bridge, where

Y is as hereinbefore defined and
n denotes the number 2, 3 or 4,

or, if D together with E denotes a group R_d, it may also denote a 2-oxo-morpholin-4-yl group which may be substituted by 1 or 2 methyl or ethyl groups,

D denotes a $-O-C_{1-4}$-alkylene group, while the alkylene moiety is linked to the group E, and

E denotes a dimethylamino, diethylamino, pyrrolidino, piperidino, morpholino, 4-methyl-piperazino- or 4-ethyl-piperazino group or

D together with E denotes a hydrogen atom,

a methoxy, ethoxy, 2-methoxy-ethoxy, 3-methoxy-propyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrofuranylmethoxy or tetrahydropyranylmethoxy group,

a cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cyclopropylmethoxy, cyclobutylmethoxy, cyclopentylmethoxy or cyclohexylmethoxy group or

a group R_d, where

R_d denotes a 2-(cyclobutyloxy)-ethoxy, 2-(cyclopentyloxy)-ethoxy, 2-(cyclopropylmethoxy)-ethoxy or 2-(cyclobutylmethoxy)-ethoxy group,

the tautomers, stereoisomers and salts thereof.

3. Bicyclic heterocycles of general formula I according to claim 1, wherein

R_a denotes a hydrogen atom,

R_b denotes a 1-phenylethyl, 3-methylphenyl, 3-chlorophenyl, 3-bromophenyl- or 3-chloro-4-fluorophenyl group,

R_c denotes a hydrogen atom,

X denotes a nitrogen atom,

A denotes a 1,2-vinylene group,

B denotes a methylene group,

C denotes a 2-oxo-morpholin-4-yl group which is substituted by a methoxymethyl, methoxyethyl, ethoxymethyl, ethoxyethyl, dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl, diethylaminoethyl, cyanomethyl or cyanoethyl group,

a 2-oxo-morpholin-4-yl group, wherein the two hydrogen atoms of a methylene group are replaced by a $-CH_2CH_2$, $-CH_2CH_2CH_2$, $-CH_2CH_2CH_2CH_2$, $-CH_2CH_2CH_2CH_2CH_2$, $-CH_2-O-CH_2CH_2$, $-CH_2-NCH_3-CH_2CH_2$, $-CH_2-NC_2H_5-CH_2CH_2$, $-CH_2CH_2-O-CH_2CH_2$, $-CH_2CH_2-NCH_3-CH_2CH_2-$ or $-CH_2CH_2-NC_2H_5-CH_2CH_2-$ bridge,

a 2-oxo-morpholin-4-yl group, wherein a hydrogen atom in the 5 position together with a hydrogen atom in the 6 position is replaced by a $-CH_2CH_2CH_2$, $-CH_2CH_2CH_2CH_2$, $-CH_2-O-CH_2$, $-CH_2-NCH_3-CH_2$, $-CH_2-NC_2H_5-CH_2$, $-CH_2-O-CH_2CH_2$, $-CH_2-NCH_3-CH_2CH_2$, $-CH_2-NC_2H_5-CH_2CH_2$, $-CH_2CH_2-O-CH_2$, $-CH_2CH_2-NCH_3-CH_2-$ or $-CH_2CH_2-NC_2H_5-CH_2-$ bridge,

or, if D together with E denotes a group R_d, it may also denote a 2-oxo-morpholin-4-yl group which is substituted by 1 or 2 methyl groups, and

D together with E denotes a hydrogen atom,

a methoxy, ethoxy, 2-methoxy-ethoxy, 3-methoxy-propyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy or tetrahydrofuranylmethoxy group,

a cyclobutyloxy, cyclopentyloxy, cyclopropylmethoxy, cyclobutylmethoxy or cyclopentylmethoxy group or

a group R_d, where

R_d denotes a 2-(cyclobutyloxy)-ethoxy, 2-(cyclopentyloxy)-ethoxy, 2-(cyclopropylmethoxy)-ethoxy or 2-(cyclobutylmethoxy)-ethoxy group,

the tautomers, stereoisomers and salts thereof.

4. Bicyclic heterocycles of general formula I according to claim 1, wherein

R_a denotes a hydrogen atom,

R_b denotes a 3-chloro-4-fluorophenyl group,

R_c denotes a hydrogen atom,

X denotes a nitrogen atom,

A denotes a 1,2-vinylene group,

B denotes a methylene group,

C denotes a 2-oxo-morpholin-4-yl group which is substituted by a methoxymethyl or methoxyethyl group, or

a 2-oxo-morpholin-4-yl group, wherein the two hydrogen atoms of a methylene group are replaced by a $-CH_2CH_2-O-CH_2CH_2-$ bridge, and

D together with E denotes a hydrogen atom, a methoxy or cyclopropylmethoxy group,

the tautomers, stereoisomers and salts thereof.

5. The following compounds of general formula I according to claim 1:

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((*R*)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,

(2) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(2-oxo-1,9-dioxa-4-aza-spiro[5.5]undec-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline and

(3) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[2-(2-methoxyethyl)-6-oxo-morpholin-4-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline,

the tautomers, stereisomers and salts thereof.

6. Physiologically acceptable salts of the compounds according to at least one of claims 1 to 5 with inorganic or organic acids or bases.

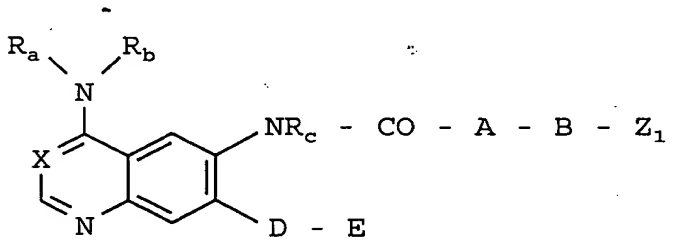
7. Pharmaceutical compositions containing a compound according to at least one of claims 1 to 5 or a physiologically acceptable salt according to claim 6 optionally together with one or more inert carriers and/or diluents.

8. Use of a compound according to at least one of claims 1 to 6 for preparing a pharmaceutical composition which is suitable for the treatment of benign or malignant tumours, for preventing and treating diseases of the respiratory tract and lungs, for treating polyps, diseases of the gastro-intestinal tract, bile duct and gall bladder as well as the kidneys and skin.

9. Process for preparing a pharmaceutical composition according to claim 7, characterised in that a compound according to at least one of claims 1 to 6 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

10. Process for preparing the compounds of general formula I according to claims 1 to 6, characterised in that

a) a compound of general formula



, (II)

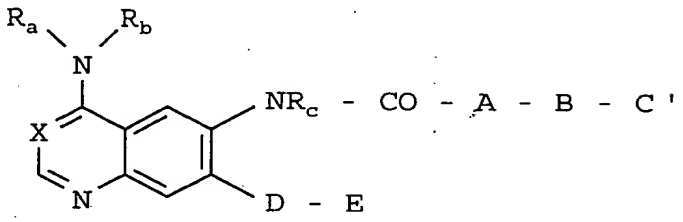
optionally formed in a reaction mixture
wherein
R_a to R_c, A, B, D, E and X are defined as in claims 1 to 5 and
Z_1 denotes a leaving group,

is reacted with a compound of general formula

H - C , (III)

wherein
C is defined as in claims 1 to 5 hereinbefore, or

b) a compound of general formula



, (IV)

optionally formed in a reaction mixture
wherein
R_a to R_c, A, B, D, E and X are defined as in claims 1 to 5 and C' denotes a correspondingly substituted N-(carboxymethyl)-N-(2-hydroxyethyl)-amino or N-(C_{1-4}-alkyloxycarbonymethyl)-N-(2-hydroxyethyl)-amino group which can be converted into a group C by cyclising, is cyclised, and

if necessary any protecting group used in the reactions described above is cleaved again and/or

if desired a compound of general formula I thus obtained is resolved into its stereoisomers and/or

a compound of general formula I thus obtained is converted into the salts thereof, particularly, for pharmaceutical use, into the physiologically acceptable salts thereof.